REMARKS/ARGUMENTS

Claims 1-21 are pending in this application. Claim 1 has been amended and support can be found, for example, on page 1, line 8. Claims 13 and 14 have been amended and support can be found in the claims and specification as originally filed.

I. Rejection under 35 U.S.C. §112, first paragraph - Definiteness

Claims 13 and 14 stand rejected under 35 U.S.C. §112, second paragraph allegedly for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner argues that the term "equivalent to" renders the claim indefinite allegedly because neither "the specification nor the claims define what conditions would be 'equivalent to' 50°C for 3 months" (page 4 of the Office Action) Applicants traverse the rejection and submit that a person of ordinary skill in the art would find the claims to be clear and definite.

A person of ordinary skill in the art would understand the "conditions that are, or are equivalent to, 50°C for 3 months" element of claims 13 and 14 based upon the Arrhenius equation. The long term stability of biological therapeutics is an important indicator of overall therapeutic quality and such information is routinely submitted to regulatory authorities. However, although actual elapsed or real time stability studies would be the most reliable demonstration of product shelf life, the length of time required for real time analysis makes it impractical. Therefore, a reliable alternative method to real time analysis is the well-established practice of accelerated stability testing based on the Arrhenius equation.

Typically, biological therapeutics in a pharmaceutical formulation degrade and lose biological activity over time as a result of a first order chemical reaction, which can be expressed mathematically as follows.

$d/Ca/dt = k.Ca$

where d/Ca/dt is the rate of change of concentration of the therapeutic with time, k is a rate constant, and Ca is the concentration of the therapeutic.

Experimental data obtained at different temperatures from these formulations can be analyzed by the Arrhenius equation, which relates to the activation energy for a particular

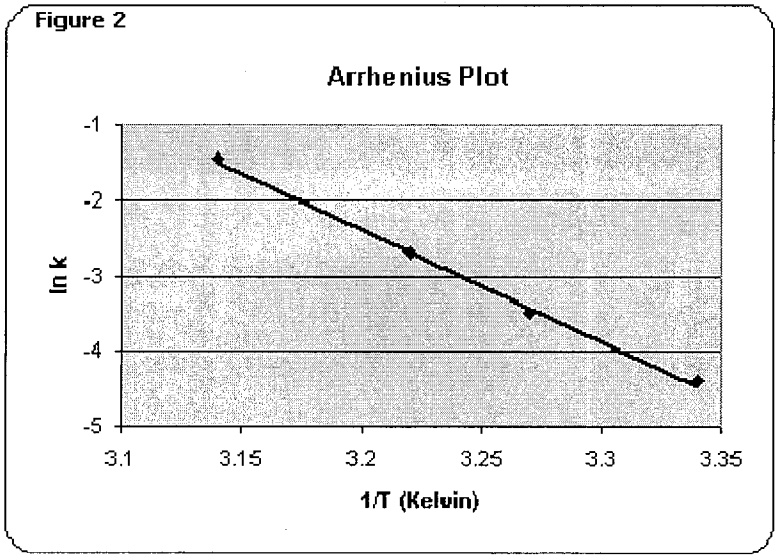
reaction to the temperature and to the first-order rate constant, k. The Arrhenius equation may be expressed as follows.

k = A.exp (-- Ea/RT) or in logarithmic form as In k = -- Ea/RT + In A

where k is the rate constant, A is the initial activity, Ea is the activation energy, R is the gas constant, and T is the absolute temperature

According to Arrhenius, for any single degradation process, the relationship between reaction rate and temperature follows a log-linear relationship between the natural log of the rate constant (In k) and the inverse of the absolute temperature (1/T). Such a plot provides the activation energy for the process. The slope of an Arrhenius plot is equal to –Ea/R, where R is the gas constant (1.987 cal/mole K) and Ea is the activation energy in cal/mole. As such, the Arrhenius equation provides a basis for determining the rate constant, i.e., shelf life, at a temperature of interest. The first order rate constant will vary with temperature and its natural logarithm can be determined at different temperatures and plotted against the reciprocal of the absolute temperature T is degrees Kelvin. For example the Arrhenius plot below can be extrapolated to determine the value of the rate constant at a temperature of interest, e.g. 4°C or 25°C.

Figure 2



(http://www.virusys.com/stability-testing/)

Once a suitable threshold for activity is determined, e.g., 80% of initial activity, the shelf life of a biological therapeutic can be determined using this calculation. As such, Applicants respectfully submit that a person of ordinary skill in the art would understand the "conditions that are, or are equivalent to, 50°C for 3 months" element of claims 13 and 14 based upon the Arrhenius equation. Applicants request the withdrawal of the rejection.

I. Rejection under 35 U.S.C. §112, first paragraph - Enablement

Claims 1-21 stand rejected under 35 U.S.C. §112, first paragraph allegedly for lack of enablement. Applicants traverse the rejection and submit that when the proper legal standard is applied, the instant specification provides sufficient disclosure to enable a person of ordinary skill in the art to make and use the invention as presently claimed.

A. The Legal Standard

According to M.P.E.P.§2164.05(a),

> 35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected" ... [and the] specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. (emphasis added)

An application's lack of incorporation by reference of information well-known in the art is "not problematic" where it is clear that a person of ordinary skill in the art would have possessed such knowledge and the relevant references are readily accessible to the public. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (affirming finding of enablement because at the time of filing of the earliest application, publications in professional journals had disclosed the relevant DNA sequence and "essential regions"). The Federal Circuit has held that "[t]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Nonetheless, enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 , 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

As discussed below, Applicants submit that one of ordinary skill in the art would be able to make and use the invention without undue experimentation. An allegation of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). These factors include: "(1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

In addition, according to MPEP §2164.06, the mere fact that an extended period of experimentation is necessary does not make such experimentation undue. *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.* It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed (*Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

B. Application of the Legal Standard

Claims 1-21 recite a dry powder composition comprising recombinant alpha 1-antitrypsin (rAAT). Applicants respectfully submit that the present specification provides sufficient detail to enable those of ordinary skill in the art to practice the full scope of dry powder compositions comprising rAAT as currently claimed because (i) the instant specification provides identifying information for rAAT, and (ii) the function, structure and sequence information for rAAT, as well as reliable protocols for testing the same, were well-known and freely accessible to those of ordinary skill in the art at the time of filing.

For instance, the present specification provides that rAAT "is a 395 amino acid protein of 44 kD, that is non-glycosylated and has an amino acid sequence identical to the human plasma

protein (AAT) with the exception of an N-acetylmethionine residue at the amino terminus" (lines 6-10, page 1). U.S. Pat. No. 5,780,014 (hereinafter referred to as the "'014 patent"), incorporated by reference into Applicant's application, discloses that alpha-1 antitrypsin is "a protease inhibitor with inhibitory activity toward neutrophil elastase." (Col 1., ll. 22-23). The '014 patent further specifies the source of alpha-1 antitrypsin (Col. 3, ll. 32-40) and incorporates by reference U.S. Pat. No. 4,599,311 (hereinafter referred to as the "'311 patent"). The '311 patent provides the genomic location and amino acid sequence of human alpha 1-antitrysin (Col. 6, ll. 17-19; Col. 7-10). The '311 patent also provides for a recombinant human alpha 1-antitrypsin that employs a yeast host and explains that the resulting polypeptide differs in degree of glycosylation from naturally occurring human alpha 1-antitrypsin (Col. 11, ll. 18-29). In addition, Travis et al. (1985) J. Biol. Chem. 260:4384-4389 (hereinafter referred to as "Travis et al.") provide experimental procedures for isolating human recombinant AAT and studying its molecular properties, including protocols for testing the proteinase inhibitory activity of rAAT polypeptides. Accordingly, the present specification need not disclose any structural or functional details regarding recombinant human alpha 1-antitrypsin because this information was well-known to those of ordinary skill in the art at the time of filing.

Applying the *In re Wands* factors to the present claims, we find the following.

1) The nature of the invention:

The nature of the invention is a dry powder composition comprising non-glycosylated recombinant human alpha 1-antitrypsin (rAAT).

2) The state of the prior art:

As discussed above, publications such as the '014 patent, the '311 patent, and Travis et al. provide information regarding the source, function, structure, and amino acid sequence of alpha 1-antitrypsin, including non-glycosylated human rAAT.

3) The relative skill of those in the art:

The relative skill of those in the art is high, one of ordinary skill in the art often having an advanced academic degree and several years of relevant experience including the needed

technical skill to practice the experimentation described in the art relating to recombinant alpha 1-antitrypsin, and dry powder compositions comprising the same.

4) The predictability or unpredictability of the art:

The predictability of biotechnological arts is generally high with regard to the production and isolation of recombinant human rAAT. The fact that it can readily be made through the use of yeast expression plasmids, as described in Travis et al. (page 4384-4385 Methods), indicates that the level of predictability of the art is high, and the experimentation required is routine rather than undue. As such, the level of predictability that suitable non-glycosylated human rAAT polypeptides could be routinely identified and utilized by those of ordinary skill in the art is high.

5) The breadth of the claims:

The claims are directed to a dry powder composition comprising non-glycosylated human rAAT. A person of ordinary skill in the art would appreciate that such rAAT can be routinely produced and identified as evidenced by the discussion above. In addition, the claims are limited in scope to dry powder compositions comprising non-glycosylated human rAAT. As such, the claims are not broad in that the subject matter is explicitly recited in the claims.

6) The amount of direction or guidance provided:

The instant specification provides sufficient direction and guidance to enable the invention as presently claimed. As discussed above, the U.S. patents and the Travis et al. paper, all publicly accessible sources, disclose the molecular identity of and detailed experimental procedures for obtaining rAAT polypeptides and testing their function. Applicant's specification provides preferred procedures for drying on page 4. Applicant also provides preferred compositions of the dry formulation on pages 3 to 4 of the specification. Applicants respectfully submit that based on the instant specification and the publicly available disclosures already discussed, one skilled in the art could easily produce, obtain and test the identity and functional properties of rAAT, including a dry powder composition comprising non-glycosylated human rAAT. As such, the specification provides sufficient guidance to a person of ordinary skill in the art to practice the present invention.

7) The presence or absence of working examples:

Applicant's specification sets forth working examples pertaining to dry powder formulations and compositions. Applicants point out to the Examiner that working examples are not even required to satisfy the enablement requirement. The U.S. Court of Customs and Patent Appeals has held that "a specification need not contain one working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." In re Borkowski, 422 F.2d 904 (CCPA 1970). The specification also incorporates by reference the working examples of the '014 patent. Applicants submit that such examples, along with the publicly accessible information contained in Travis et al., provide adequate guidance to a person of ordinary skill in the art to practice the present invention without undue experimentation.

8) The quantity of experimentation necessary:

The amino acid sequences and protocols for producing and testing the function of non-glycosylated, human rAAT are well-known and publicly available to those of ordinary skill in the art. Indeed, as discussed above, the functional and structural criteria for such rAAT are so well-defined in the field that a practitioner of the invention need not conduct any experimentation to obtain rAAT because it may reliably be obtained using well-known protocols. Methods for producing dry powder compositions are also well-known and publicly available to those of ordinary skill in the art. Given the disclosure of preferred compositions and dry methods in the present specification, it is believed that no undue amount of experimentation is required to practice the invention as presently claimed.

Thus, in view of the above, since the disclosures in the specification, nature of the invention, state of the prior art, and relative skill in the art enable one of ordinary skill in the art to reliably produce a dry powder composition of recombinant alpha 1-antitrypsin; since the predictability of biotechnological arts is generally high regarding the identification and production of such compositions; since the claims are not broad in that the subject matter claimed is explicitly recited in the claims, Applicants submit that the quantity of experimentation needed to practice the invention is not undue and that the specification enables one of ordinary skill in the art to make and use the invention to the full scope of the claims.

Response to Examiner's Arguments

The Examiner asserts that the instant invention "encompasses dry powder compositions comprising any alpha 1-antitrypsin protein having any structure and any function" and that claims 1-21 are "so broad as to encompass any dry powder composition comprising any alpha 1-antitrypsin protein having any function and any structure" (page 5 of the April 10, 2008 Office Action). The Examiner bases these assertions on the alleged failure of the specification to establish:

> "(A) the function of all proteins encompassed within the claims; (B) the structure of all proteins encompassed within the claims; (C) regions of the protein structure which may be modified without affecting the desired activity; (D) the general tolerance of the desired activity to modification and extent of such tolerance; (E) a rational and predictable scheme for choosing which, of the unlimited number of proteins, have the desired properties; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful." (*Id.* at 6).

Applicants respectfully submit that the Examiner has not applied the legal standard for enablement correctly. Applicants are not legally required to disclose specific structures, amino acid sequences, functional definitions, regions amenable to modification, the extent of tolerance to modification and schemes for choosing desired proteins in a specification when such information is incorporated by reference, well known, and publicly accessible. Indeed, including in exhaustive detail that which is duplicative of information well known in the art would contravene the above-cited MPEP instructions to "preferably omit" well-known and publicly available information. As discussed in detail above, the function, structure, amino acid sequence, and step-by-step protocols for obtaining non-glycosylated human rAAT are well known and accessible from public sources, some of which were incorporated by reference into the instant specification. Therefore, Applicants respectfully submit that the detailed protocols for isolating rAAT as set forth in Travis et al. rebut Examiner's assertion that such isolation is "not routine in the art" and "unpredictable" (*Id.*).

Also, as discussed above, typical compositions and protocols for obtaining dry powder formulations are well known and publicly accessible. Thus, the specification and prior art do not teach "any" dry powder comprising rAAT of "any" structure or "any" function, but instead teach

specific parameters that provided a scope of enablement that is in line with the scope of the claims. When the information from the prior art is combined with general disclosure as to drying methods and composition content parameters in the instant specification (pages 2 to 7), a person of ordinary skill in the art is clearly taught how to make and use the full scope of the claimed invention without undue experimentation.

Moreover, Applicants respectfully submit that the Examiner has improperly interpreted the term "recombinant human alpha 1-antitrypsin". For instance, the Examiner has asserted that the pending claims "are so broad as to encompass any dry powder composition comprising any alpha 1-antitrypsin protein having any function and any structure." (page 5 of the Office Action) Applicants respectfully disagree and submit that this implies limitless modifications to the structure and function of "recombinant human alpha 1-antitrypsin" that can never be reached. This absolute standard is inconsistent with the legal standard for enablement of composition claims in the United States, which requires that claims must be " given their broadest reasonable interpretation consistent with the specification. In re Hyatt, 211 F.3d 1367, 1372 (Fed Cir. 2000); Philips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005). See also M.P.E.P. §2111. Moreover, the Examiner's burden regarding the enablement requirement has been clearly set forth in M.P.E.P. §2164.04:

> Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. For terms that are not well-known in the art, or for terms that could have more than one meaning, it is necessary that the examiner select the definition that he/she intends to use when examining the application, based on his/her understanding of what applicant intends it to mean, and explicitly set forth the meaning of the term and the scope of the claim when writing an Office action. See *Genentech v. Wellcome Foundation,* 29 F.3d 1555, 1563-64, 31 USPQ2d 1161, 1167-68 (Fed. Cir. 1994).

Applicants respectfully submit that a person of ordinary skill in the art would understand "non-glycosylated recombinant human alpha 1-antitrypsin" to have its ordinary meaning, *i.e.*, a protease inhibitor with inhibitory activity toward neutrophil elastase (Col. 1, ll. 22-23 of the '014 patent) having the amino acid sequence shown in Col. 7-10 of the '311 patent. This ordinary meaning is consistent with Applicants' disclosure regarding rAAT, *i.e.*, a 395 amino acid protein of 44 kD, that is non-glycosylated and has an amino acid sequence identical to the human plasma protein (AAT) with the exception of an N-acetylmethionine residue at the amino terminus. (page

1, lines 6-10). Such an interpretation is broad enough to encompass any dry powder composition comprising any alpha 1-antitrypsin protein having any function and any structure, but certainly is not limited to that extreme. Applicants request that the Examiner substitute an interpretation of "recombinant human alpha 1-antitrypsin" in line with what Applicants intended it to mean, and what one of ordinary skill in the art would consider reasonable.

Based on the foregoing, Applicants accordingly submit that the rejection of claim 1, and all claims depending therefrom, under 35 U.S.C. § 112, first paragraph are overcome, and the Examiner is respectfully requested to reconsider and withdraw these rejections.

II. Rejection under 35 U.S.C. §112, first paragraph – Written description

Claims 1-21 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse the rejection and submit that when the proper legal standard is applied, it is clear that the instant specification reasonably conveys to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language" (*In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983; S*ee also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. (*See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil*

v. Atlantic Richfield Co., 208 F.2d 989, 996 (Fed. Cir. 2000; *See also* M.P.E.P. §2163 II(A)). It is clear that the Examiner must take into account the nature of the invention and level of knowledge in the relevant art in determining whether a claim meets the written description requirement. This standard is outlined in M.P.E.P. § II A. 3. (a) i) (C) (2), which states that

> the description needed to satisfy the requirements of 35 U.S.C. 112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar*, 418 F.3d at 1357, 76 USPQ2d at 1084.

The decision by the U.S. Court of Appeals for the Federal Circuit in *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005) is particularly instructive because the Court addressed the written description requirement for inventions directed to combinations of "selected DNA segments" as disclosed in U.S. Patent No. 6,407,221 (the "'221 patent") U.S. Application 08/084,994 (the "'994 application") (*Id.* at 1352). The present invention is also directed to recombinant human alpha 1-antitrypsin having a known DNA and amino acid sequence rather than to a novel DNA sequence.

Applicants submit that the written description issues decided in *Capon* are analogous to the written description issues pending in the instant case, namely (i) whether the state of scientific knowledge, as explained in the Applicants' specification, was considered; (ii) the application of a *per se* rule requiring recitation in the specification of structural details or amino acid sequences, when those sequences are already known in the field, and (iii) whether the generic concept of the invention was properly considered. In *Capon*, the Federal Circuit reversed an analogous written description rejection by the Board of Patent Appeals and Interferences of the U.S. Patent and Trademark Office (hereinafter the "Board"). Accordingly, based on the following, the Applicants respectfully request that the written description rejection be withdrawn and the instant case be passed to issue.

A. *Capon v. Eshhar*

In its decision, the Federal Circuit reversed the Board's finding that the specifications at issue did not meet the written description requirement because they did not reiterate the nucleotide sequences of the claimed chimeric molecules.

(1) Claims

As discussed above, the '221 patent and the '994 application each contained claims directed to chimeric DNA encoding a fusion polypeptide that contains an scFv linked to a lymphocyte signaling protein to create a chimeric scFv-receptor ("scFvR") that upon expression in a cell, combines the specificity of an antibody with the tissue penetration, cytokine production, and target-cell destruction capability of a lymphocyte (*Capon*, 418 F.3d at 1352). The Federal Circuit noted the explanation by both patentees that "their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result." [emphasis added] (*Capon*, 418 F.3d at 1358).

(2) Written description rejection

In Capon, the Federal Circuit reviewed the Board's conclusion that the specifications of the '221 patent and the '994 application did not meet the written description requirement to support their corresponding claims. The Federal Circuit first noted the Board's statement that

> the full scope of novel chimeric DNA the parties claim is not described in their specifications under 35 U.S.C. § 112, first paragraph, by reference to contemporary and/or prior knowledge in the art of the structure, formula, chemical name, or physical properties of many protein domains, and/or DNA sequences which encode many protein domains, which comprise single-chain proteins and/or DNA constructs made in accordance with the plans, schemes, and examples thereof the parties disclose. [emphasis added] (*Id.* at 1354-55).

Then, the Federal Circuit summarized the Board's conclusion as follows:

> both Eshhar and Capon claim novel genetic material described in terms of the functional characteristics of the protein it encodes. Their specifications do not satisfy the written description requirement because persons having ordinary skill in the art would not have been able to

> visualize and recognize the identity of the claimed genetic material without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results. (*Id.* at 1355).

In addition, the Federal Circuit considered whether the specifications adequately supported the breadth of all the claims. The Court noted the Board's failure to discuss the patentees' generic concept of "selecting and combining a gene sequence encoding the variable domain of an antibody and a sequence encoding a lymphocyte activation protein, into a single DNA sequence which, upon expression, allows for immune responses that do not occur in nature." (*Id.* at 1360). Furthermore, the Federal Circuit stated that the "record does not show this concept to be in the prior art, and includes experimental verification as well as potential variability in the concept." (*Id.*).

(3) Legal analysis

The Federal Circuit rejected the Board's written description rejection because of its (i) failure to consider the state of scientific knowledge, as explained by the patentees; (ii) application of a *per se* rule requiring recitation in the specification of structural details or amino acid sequences, when those sequences are already known in the field, and (iii) failure to consider the generic concept described by the patentees, which is not in the prior art, and includes experimental verification, as well as potential variability.

(a) State of scientific knowledge

The Federal Circuit provided the relevant legal standard for determining compliance with the written description requirements under 35 U.S.C. § 112, first paragraph, first noting that the "descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." (*Id.* at 1357). In addition, the Federal Circuit stated that since the "law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science." (*Id.*).

As discussed above, the patentees' invention was not the discovery of the individual DNA segments that made up the chimeric molecules, but rather the novel combination of segments to achieve a novel result. This was established during the interference proceeding by expert testimony pertaining to the nature of the invention and level of knowledge in the relevant art. The experts explained that "the principle of forming chimeric genes from selected segments of DNA was known, as well as their methods of identifying, selecting, and combining the desired segments of DNA." (*Id.* at 1355). In addition, the experts explained that "the prior art contains extensive knowledge of the nucleotide structure of the various immune-related segments of DNA" (*Id.*).

In addition, the Court noted the patentees' statements that "persons experienced in this field would readily know the structure of a chimeric gene made of a first segment of DNA encoding the single chain variable region of an antibody, and a second segment of DNA encoding an endogenous protein ... [,] re-analysis to confirm these structures would not be needed in order to know the DNA structure of the chimeric gene ... [,] and that the Board's requirement that the specification must reproduce the 'structure, formula, chemical name, or physical properties' of these DNA combinations had been overtaken by the state of the science." [emphasis added] (*Id.* at 1356). In addition, the patentees stated that "where the structure and properties of the DNA components were known, reanalysis was not required." (*Id.*)

Following its discussion of expert testimony, the Federal Circuit clearly stated that a legal determination of written description must "take cognizance of the scientific facts" and found that the Board had

> erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. [emphasis added] (*Id.*)

(b) Improper per se rule

The Federal Circuit also rejected the Board's application of a *per se* rule as to the disclosure of sequence information for known molecules. In particular, the Court stated that the

> Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. [emphasis added] (*Id.* at 1358).

With respect to the Board's conclusions regarding the disclosure of sequence information, the Federal Circuit held that the

> Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance [and the] Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes. [emphasis added] (*Id.*)

(c) Failure to consider the generic concept of the invention

The Federal Circuit also considered the issue of claim scope, noting that the Board had "objected that the claims were broader than the specific examples" and that it failed to "relate any of the claims ... to the examples" (*Id.* at 1356). However, the Court indicated that "the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter." (*Id.* at 1359). Furthermore, the Federal Circuit stated that it is "not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic claim." (*Id.*).

In light of the disclosure, the Federal Circuit faulted the Board's failure to properly consider the generic concept described by the patentees, namely the combination of nucleotide sequences encoding an antibody variable domain and a lymphocyte activation protein into a single DNA sequence which, upon expression, allow for immune responses that do not occur in nature. Significantly, the Federal Circuit found that the "record does not show this concept to be in the prior art, and includes experimental

verification as well as potential variability in the concept." [emphasis added] (*Id.* at 1360).

In summary, the Federal Circuit reversed the Board decision regarding written description because it (i) improperly imposed a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field; and (ii) failed to explore the support for the claims, in view of the specific examples and general teachings in the specification and the known science. (*Id.* at 1360-61).

(4) *Falkner v. Inglis*

In addition, the Federal Circuit held in *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006) that the recitation of known structure is not required for written description, relying heavily on the *Capon* decision. In the *Falkner* decision, the Federal Circuit clearly indicated that known sequences need not be recited in an Applicant's specification, stating that

> it is the binding precedent of this court that Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art ... [and when] the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh." (citing *Capon v. Eshhar*) [emphasis in original] (*Falkner*, 448 F.3d at 1367).

Furthermore, the Court in *Falkner* acknowledged that the recitation of known sequence information would not serve the purpose of the written description requirement. In particular, the Federal Circuit stated that

> a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention. [emphasis added] (*Id.* at 1368).

Finally, the Federal Circuit held that the disclosure of sequence information in the scientific literature obviated the need to recite or incorporate by reference such information in the specification. In the words of the Court,

> the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences. [emphasis added] (*Id.*).

In summary, the Federal Circuit in *Falkner* found that a recitation of known sequence information in a specification serves no purpose for complying with the written description requirement, and in fact adds unnecessary bulk to the specification.

B. The Present Application

Applicants submit that the invention, the nature of the written description rejection, and the legal analysis in the *Capon* and *Falkner* decisions are analogous to those of the present case. Applicants submit that in the instant application, (i) the claims are directed to a novel dry powder composition comprising non-glycosylated recombinant human alpha 1-antitrypsin; (ii) the Examiner has failed to consider the state of scientific knowledge; (iii) the Examiner has improperly applied a *per se* rule requiring recitation in the specification of the structural details or amino acid sequences, when those sequences are already known in the field, and (iv) the Examiner has failed to properly consider the generic concept of the Applicants' invention.

As such, the Examiner's written description rejection and legal analysis in the present application retains all the flaws of the reversed Board rejections in *Capon* and *Falkner*. Accordingly, the written description rejection asserted by the Examiner should be withdrawn.

(1) Claims

The present application's claims are directed to a dry powder composition comprising non-glycosylated recombinant human alpha 1-antitrypsin (rAAT). Applicants submit that, similar to *Capon*, the Applicants' invention is not in discovering rAAT or dry powder compositions or the function of AAT in general, for these are in the prior art, but in the novel combination of elements to achieve a novel result of overcoming obstacles to long-term stability unique to recombinant, as opposed to natural, alpha 1-antitrypsin. The invention recited in the currently pending claims is a novel combination achieving a novel result because, as discussed below, the prior art does not disclose a dry powder composition comprising non-glycosylated, recombinant human alpha 1-antitrypsin. As such, the composition recited in currently amended claim 1 is analogous to the DNA combination recited in the claims of the '221 patent and the '994 application. Therefore, the legal standards and analysis of *Capon* and *Falkner* readily apply in the instant application.

(2) Written description rejection

The Examiner has rejected claims 1-21 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner states that the Applicants'

> claims are directed to dry powder compositions comprising any one of a genus of human alpha 1-antitrypsin proteins. The specification teaches the structure of no single representative species of such proteins. Moreover, the specification fails to describe the enzymatic, biological, or cellular function of said proteins. (page 7 of the April 10, 2008 Office Action).

(3) Legal analysis

Applicants reiterate that the Examiner has committed the same errors in legal reasoning as the Board in Capon, namely the (i) failure to consider the state of scientific knowledge; (ii) application of a *per se* rule requiring recitation in the specification of structural details or amino acid sequences, when those sequences are already known in the field, and (iii) the failure to properly consider the generic concept of the invention.

(a) State of scientific knowledge

Applicants submit that similar to the Board in *Capon*, the Examiner failed to consider the state of the scientific knowledge, namely the Applicants' recitation of relevant references (Travis et al., the '014 patent, and the '311 patent) disclosing the functional and amino acid sequence information for rAAT. Therefore, the instant specification refers to structural and functional information in the public domain, including protocols for producing and testing rAAT function. The '311 patent likewise discloses functional and structural information for rAAT. Applicants submit that similar to *Capon*, persons experienced in this field would readily know the structure and function of human rAAT, including "representative species" of rAAT; therefore re-analysis to confirm these structures would not be needed in order to know the amino acid structure of human rAAT. As such, the Examiner's requirement that the instant specification must reproduce functional, structural or amino acid sequence information of rAAT has been overtaken by the state of the science, and where the structure and properties of the polypeptides are known, reanalysis is not required.

In summary, Applicants have recited numerous publications indicating that the state of scientific knowledge is such that the instant specification provides sufficient description of the structural and functional knowledge regarding rAAT. Applicants respectfully submit that the Examiner has erred in refusing to consider the state of scientific knowledge, and upon a proper consideration of this knowledge the Examiner's requirement for functional, structural or amino acid sequence information of known polypeptides is not proper.

(b) Improper per se rule

The Examiner argues that the Applicants have not provided the structure of any "representative species encompassed by the genus" of human alpha 1-antitrypsin proteins or "the enzymatic, biological, or cellular function" of said proteins, and therefore the claims stand rejected. Applicants respectfully submit that, similar to the Board in *Capon*, the Examiner has rejected the claims based on a *per se* rule requiring the recitation of functional information and structural information or nucleotide sequences of the present invention when this information is already known in the field. This functional and

structural information is described in the publications referred to by the Applicants in the instant specification. Moreover, the *Falkner* decision makes it abundantly clear that the Examiner's insistence that the Applicants recite known sequence information does not serve the goals of the written description requirement, and therefore such re-description is not required.

(c) Failure to consider the generic concept of the invention

As previously discussed, the Examiner argues that the Applicants' specification (i) does not adequately describe the structure of any "representative species" of human alpha 1-antitrypsin and (ii) does not provide the function of human alpha 1-antitrypsin. Applicants submit that, like the Board in *Capon*, the Examiner has erred in failing to consider the generic concept of the Applicants' invention, namely the dry powder composition comprising non-glycosylated, human rAAT, which overcomes stability obstacles specific to recombinant, as opposed to natural, AAT. Furthermore, Applicants submit that the Applicants' invention is not in the prior art.

According to *Capon*, the support for Applicants' generic claims depends on multiple factors, including the existing knowledge in the particular field, and the extent and content of the prior art. Applicants respectfully submit that the Examiner has not properly considered the support for these claim terms, in view of the specific examples and general teachings in the specification and the known science. The instant specification incorporates by reference structural and functional information related to both natural and recombinant AAT, and describes the use of well-known procedures for testing rAAT function and formulating a dry powder composition of recombinant AAT. The Examples section describes compositions created using well-known techniques, and describes well-known techniques for measuring both conformational and acute stability. In addition, it is clear from the Applicants' arguments below that this concept is not in the prior art.

In summary, based on the clear parallels between the instant case, and the *Capon* and *Falkner* decisions, Applicants submit that the written description rejection is improper because the Examiner has (i) failed to consider the state of scientific

knowledge; (ii) improperly applied a *per se* rule requiring recitation in the specification of the functional and structural details or amino acid sequences of molecules that are already known in the field, and (iii) failed to properly consider the generic concept of the Applicants' invention. As such, Applicants request the withdrawal of the written description rejection.

III. Rejection under 35 U.S.C. §102(b) - Anticipation

Claims 1-19 and 21 have been rejected under 35 U.S.C. §102(b), allegedly for being anticipated by Eljamal et al. (U.S. Pat. No. 5,780,014). The Examiner asserts that

> Eljamal et al. teach a dry powder composition comprising recombinant human alpha 1-antitrypsin... optionally with a salt and a buffer of neutral pH... The dry powder composition of Eljamal et al. also optionally comprises, a reducing agent, an anti-oxidant, and/or a chelating agent... Eljamal's composition is desiccated... and is stable after drying at 80° C. and then storage at room temperature for 9 months. (page 8, April 10, 2008, Office Action).

Applicants traverse the rejection and submit that when the proper legal standard is applied, Eljamal et al. cannot anticipate the currently pending claims.

A. The Legal Standard

The Federal Circuit has stated that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Further, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

B. The Present Invention

As currently amended, claim 1 recites a dry powder composition comprising non-glycosylated recombinant human alpha 1-antitrypsin (rAAT). By contrast, Eljamal et al. discloses "purified human plasma α1AT was supplied by Armour Pharmaceutical Co." was used to make a powder composition (Col. 10, lines 38-52; Example 1), thereby

limiting the reference to natural AAT, which is known to be glycosylated. In addition, as evidenced by the '311 patent discussed above, natural purified AAT differs from rAAT in the degree of glycosylation (Col. 11, ll. 18-29). Therefore, Eljamal et al. does not disclose each and every element of the currently pending claims because it fails to disclose a recombinant AAT or a non-glycosylated AAT. As the reference does not disclose each and every element of the currently pending claims, it cannot be used to assert an anticipation rejection.

IV. Rejection under 35 U.S.C. §103(a)

Claim 20 stands rejected as being allegedly unpatentable over Eljamal et al. (U.S. Pat. No. 5,780,014) in view of Millqvist-Fureby et al. (1999) Int'l. J. Pharmaceutics, 188:243-253. The Examiner relies upon Eljamal et al. for the reasons described above and cites Milqvist-Fureby et al. as allegedly teaching "a dry powder composition comprising an enzyme and a surfactant" (page 8 of the Office Action). Based upon this, the Examiner concludes that it "would have been obvious to a person of ordinary skill in the art to combine the teachings of Eljamal et al and Millqvist-Fureby et al to produce a dry powder composition comprising recombinant human alpha 1-antitrypsin and a surfactant." (page 9 of the Office Action). Applicants respectfully disagree and traverse the rejection.

An obviousness inquiry is controlled by the factors articulated by the Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of non-obviousness. In addition, a long line of Federal Circuit decisions has established that a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person of ordinary skill in the art provides some motivation or suggestion to combine the prior art teachings (the "teaching, suggestion, or motivation" or "TSM" test). While the Supreme Court has recently rejected a rigid application of the TSM test, it stated that the Graham Deere factors still control an obviousness inquiry. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Moreover, the Court indicated that there is

"no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." KSR, 127 S. Ct at 1731. The Court specifically acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.*

Applying these principles, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because **(A)** the references cited do not teach all limitations of the currently pending claims, and **(B)** there is no reasonable expectation of success.

(1) No teaching of each and every claim element.

As discussed above, Eljamal et al. does not teach a recombinant or a non-glycosylated AAT polypeptide, as recited in currently amended claim 1. Claim 20 depends from claim 1 and therefore contains all the limitations of claim 1. Therefore, Applicants' arguments above concerning the lack of disclosure in Eljamal et al. also apply to this rejection.

Millqvist-Fureby et al. fails to cure the defects of Eljamal et al. because it is limited to the analysis of crystalline porcine trypsin 4500 K, which is manufactured by the extraction of its inactive precursor, trypsinogen, from porcine pancreatic tissue (see Novozymes product information sheet). As such, the trypsin disclosed in Millqvist-Fureby et al. is not recombinant, nor is there any indication it is non-glycosylated. As such, there is no teaching in either reference of a recombinant or a non-glycosylated AAT polypeptide.

As the reference fails to teach or suggest certain elements of Applicants' presently claimed invention, it do not teach or suggest each of the elements of the currently pending claims.

(2) No reasonable expectation of success.

Applicants submit that there is no reasonable expectation that a modification of the natural AAT disclosed in Eljamal et al. to reach the stable formulation of rAAT provided in the present application would be successful. The difference between recombinant and natural AAT is significant because Travis et al. (1985) discloses that the stabilization of rAAT is more difficult than stabilization of natural AAT; with rAAT having a half-life that is considerably less than that of natural AAT (p. 4338). The Applicants' invention, as presently claimed, is based at least on the concept that dry powder compositions comprising non-glycosylated, recombinant human AAT can achieve good stability-comparable to dry powder compositions of natural AAT. Applicants submit that at the time of filing, there was no evidence of the advantages of a dry powder composition of non-glycosylated recombinant alpha 1-antitrypsin.

As to Examiner's assertion that Eljamal et al. discloses 9 month storage at room temperature, Applicants respectfully submit that this disclosure does not apply to the claims of the present invention. The storage data in Eljamal et al. pertains to natural AAT, while Applicants claims are directed to recombinant AAT. As discussed above, it is know in the art that recombinant AAT is not stabilized as easily as natural AAT. Applicants submit that the modification of Eljamal et al. proposed by the Examiner has no reasonable expectation of success.

In light of the foregoing, Applicants submit that the Examiner has not established a prima facie case of obviousness and request the withdrawal of the rejection.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **50-4634** (referencing Attorney's Docket No. **ARR-0037-1.US (123887-182053)**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Goodwin|Procter LLP

Date: October 10, 2008

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